MALARIA

Malaria, a serious disease caused by parasites of the genus *Plasmodium* and transmitted by a mosquito, continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Globally, malaria causes more than 1 million deaths each year. Approximately 60 percent of malaria deaths occur in the poorest 20 percent of the total global population, with the majority of deaths occurring in children aged 5 years and younger in sub-Saharan Africa.[43] Unfortunately, variations in the parasite that cause malaria have made the development of a successful vaccine very difficult.

Malaria research at the NIH dates back to the 1930s, when malaria was still a major public health problem in the United States. NIAID is currently one of the world's leading supporters of malaria research. NIAID maintains a broad malaria research portfolio that includes parasite biology, pathogenesis, drug development, vaccine development, epidemiology, and vector control. NIAID-funded malaria research is conducted by scientists at institutions throughout the United States, including NIAID's own intramural laboratories, and overseas.

NIAID's large malaria research program is centered in the Malaria Vaccine Development Branch (MVDB). The MVDB collaborates with a number of investigators within the United States and throughout the world as well as with the extramural NIH malaria program and with a variety of funding agencies, such as the U.S. Agency for International Development (USAID) and the Gates Malaria Vaccine Initiative. The MVDB has produced six vaccine candidates using the quality control practices required for manufacturing clinical materials, three of which are in phase I clinical trials. MVDB researchers also are collaborating on phase I testing in Mali of another vaccine candidate called FMP1, and investigational new drug applications are being prepared for three more vaccine components; several others are under development. If any of these vaccine formulations are found to be safe and capable of eliciting an immune response, further phase I and phase II testing will be conducted in collaboration with colleagues at the NIAID-supported Malaria Research and Training Center in Mali, West Africa, or at other suitable field sites. In the past year, MVDB researchers and their Malian colleagues made considerable progress in building a field vaccine testing capability and in establishing the baseline epidemiology for the evaluation of phase II clinical trials.

Intramural investigators also are conducting basic studies aimed at providing fundamental biological information for the development of diagnostics, therapeutics, and other control measures against the disease. For example, Division of Intramural Research scientists are using the malaria parasite genome databases and microarray analysis to identify genes that may be involved in drug resistance and parasite sexual development. Identifying these genes is an important step in developing measures to interrupt parasite transmission and will provide critical information for drug and vaccine development. In addition, to understand the factors that determine the severity of malaria, NIAID investigators are studying how hemoglobin C and hemoglobin S (sickle-cell hemoglobin) protect children from severe and fatal complications of malaria caused by *Plasmodium falciparum.*

Through its extramural malaria research program, NIAID also supports extensive research on malaria vaccines conducted by researchers from academia and industry. The Institute currently funds multiple studies aimed at developing vaccines against different stages of the malaria parasite and has conducted phase I and phase II clinical trials of several of the most promising candidates. These research efforts represent a critical component of NIAID's Research Plan for Malaria Vaccine Development, which is designed to accelerate research leading to the development of malaria vaccines. Under a contract with Science Applications International, NIAID established a capability to undertake targeted research essential to translating basic research concepts into prototype vaccine products for clinical evaluation. Recent activities included process development for production of novel candidate vaccines, production and qualification of critical reagents for quality control of new candidate vaccines, and preclinical safety evaluation of promising candidate vaccines prior to entry into clinical trials.

In June 2003, NIAID launched its first trial of a candidate malaria vaccine in Mali. This trial exemplifies a key component of the NIAID Research Plan for Malaria Vaccine Development, which is to establish research centers in malaria-endemic areas that can support clinical testing and development of malaria vaccines. The trial is the result of many years of effort by a group of organizations dedicated to creating an effective malaria vaccine. In addition to NIAID extramural and intramural scientists and the University of Bamako in Mali, collaborators include the University of Maryland at Baltimore; NIAID's Malaria Vaccine Development Section; the Malian Ministries of Health and Education; the Walter Reed Army Institute of Research; GlaxoSmithKline Biologicals; USAID; and the World Health Organization.

NIAID-supported researchers continue to identify, validate, and evaluate new antimalarial therapies and vector-control approaches in an effort to develop new compounds and strategies for malaria treatment and prevention. In 2003, NIAID supported a phase I clinical trial of a chloroquine-analog effective against chloroquine-resistant *P. falciparum* as well as investigator-initiated research on preclinical development and evaluation of novel compounds. NIAID also supports grants focused on vector-control strategies, including a project aimed at mitigating insecticide resistance and one that seeks to develop new environmentally safe insecticides targeting mosquito activities.